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Conjugation of succinic acid to non-ionogenic amphiphilic polymers modulates their interaction with cell plasma membrane and reduces cytotoxic activity

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ABSTRACT

Pluronic block copolymers L61 and L121 were reacted with succinic anhydride to produce, respectively, their mono- and bisderivatives with succinic acid. The critical micelle concentration of Pluronics decreased after modification. The modification of Pluronic L61 promoted its association with the plasma membrane of human cells and increased membrane damage, while the membranotropic activity of modified Pluronic L121 reduced compared to the initial copolymer. Modified Pluronics interfered with the viability, apoptosis induction and metabolism of A549 cells and skin fibroblasts to a much lesser extent presumably due to the introduction of succinic acid residue inhibited intracellular penetration of copolymers. Modified Pluronic L121 promoted the cellular uptake of doxorubicin and rhodamine 123 in A549 cells attributed to the inhibition of membrane P-glycoprotein. Our study provides an approach to assessing the mechanism of interaction of amphiphilic polymers with living cells and demonstrates that Pluronic–succinic acid conjugates can be used as safe and efficient modulators of intracellular drug delivery.

1. Introduction

To date, biomedical science has generated a vast number of active substances in the treatment of a variety of human diseases. In clinical trials the biological safety, and/or efficiency of the substances developed was often not proven [1]. One of the main reasons is that exogenous substances naturally possess a limited ability to pass through the body's barriers, resulting in their insufficient therapeutic concentration at organ-tissue/cellular levels. The use of adjuvant compounds to improve pharmacokinetics and facilitate intracellular delivery of existing therapeutics is becoming a topical approach in drug development [2,3].

Both natural and synthetic polymers provide an efficient tool in promoting the delivery of drugs to their cellular targets. Such polymers are generally designed as inert carriers that allow: increasing circulation time, a stability of administered drugs and the improvement of their biodistribution [3,4]. In particular, covalent conjugates of cytostatic agents with N-(2-hydroxypropyl) methacrylamide and polyglutamic acid have been introduced to suppress tumor growth [5]. Modification of peptide and oligonucleotide-based therapeutics with polyethylene glycol (PEG) has become a common route to improving their biological properties [6,7].

Another concept is that some synthetic polymers can be used as efficient modulators of biological response at cellular and molecular level rather than as inert drug carriers [8,9]. A promising class of such biologically active polymers is non-ionogenic amphiphilic polyethers, specifically tri-block copolymers of ethylene oxide (EO) and propylene oxide (PO) with the general formula $(EO)_x$–$(PO)_y$–$(EO)_x$ (Pluronics™). Depending on the hydrophilic–lipophilic balance (HLB) and molecular weight (MW), these polyethers exhibit different biological effects. Pluronics of low and medium HLB, e.g. Pluronics L61 and P85, were shown to substantially facilitate the accumulation of fluorophores and small drug molecules in human cells that overproduce membrane efflux transporters, e.g. multidrug resistance protein 1 (P-glycoprotein) [8–10]. High expression of P-glycoprotein in multidrug-resistant (MDR) cancer cells and brain capillary endothelial cells leads to the rapid exclusion of many xenobiotics including cytotoxic drugs taken into the cell [8,11].

Possible ways of Pluronic-medicated intracellular drug delivery include: facilitating the passive diffusion of a substance across the cell plasma membrane, the promotion of lysosomal release, and the inhibition of P-glycoprotein ATPase activity by altering the membrane fluidity and/or the suppression of adenosine-5′-triphosphate (ATP) production in mitochondria [8,9]. The inhibition of the efflux transporter, such as P-glycoprotein is believed to especially

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